

# Impact of Plasma Transfusion in Trauma Patients Who Do Not Require Massive Transfusion

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**BACKGROUND:** For trauma patients requiring massive blood transfusion, aggressive plasma usage has been demonstrated to confer a survival advantage. The aim of this study was to evaluate the impact of plasma administration in nonmassively transfused patients.

**STUDY DESIGN:** Trauma patients admitted to a Level I trauma center (2000–2005) requiring a nonmassive transfusion (<10 U packed RBC [PRBC] within 12 hours of admission) were identified retrospectively. Propensity scores were calculated to match and compare patients receiving plasma in the first 12 hours with those who did not.

**RESULTS:** The 1,716 patients (86.1% of 1,933 who received PRBC transfusion) received a nonmassive transfusion. After exclusion of 31 (1.8%) early deaths, 284 patients receiving plasma were matched to patients who did not. There was no improvement in survival with plasma transfusion (17.3% versus 14.1%;  $p = 0.30$ ) irrespective of the plasma-to-PRBC ratio achieved. However, the overall complication rate was significantly higher for patients receiving plasma (26.8% versus 18.3%, odds ratio [OR] = 1.7; 95% CI, 1.1–2.4;  $p = 0.016$ ). As the volume of plasma increased, an increase in complications was seen, reaching 37.5% for patients receiving >6 U. The ARDS rate specifically was also significantly higher in patients receiving plasma (9.9% versus 3.5%, OR = 3.0; 95% CI, 1.4–6.2;  $p = 0.004$ ). Patients receiving >6 U plasma had a 12-fold increase in ARDS, a 6-fold increase in multiple organ dysfunction syndrome, and a 4-fold increase in pneumonia and sepsis.

**CONCLUSIONS:** For nonmassively transfused trauma patients, plasma administration was associated with a substantial increase in complications, in particular ARDS, with no improvement in survival. An increase in multiple organ dysfunction, pneumonia, and sepsis was likewise seen as increasing volumes of plasma were transfused. The optimal trigger for initiation of a protocol for aggressive plasma infusion warrants prospective evaluation. (J Am Coll Surg 2010;210:957–965. © 2010 by the American College of Surgeons)

In the acute resuscitation of critically ill trauma patients who have sustained blood loss, there has been a shift toward aggressive use of blood component therapy.<sup>1–5</sup> Driven by

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an increasing evidence base derived from both military<sup>6–8</sup> and civilian experience,<sup>9–17</sup> aggressive plasma infusion in particular has become widely practiced. For patients who require a massive transfusion, defined in the majority of published research protocols as  $\geq 10$  U packed RBC (PRBC) within the first 6 to 24 hours, plasma infusion in ratios approaching 1:1 has been associated in multiple retrospective studies with an improvement in survival.<sup>6–17</sup>

For patients who do not require a massive transfusion, however, the impact of early plasma transfusion is unknown. The concept that plasma be used early even in patients who do not require a massive transfusion is not unreasonable, considering the survival advantage conferred by plasma transfusion in patients who do end up requiring a massive transfusion, as well as our increasing understanding of the impact of crystalloid and albumin resuscitation in the injured patient.<sup>2,3,18–22</sup> This is bolstered even further

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**Abbreviations and Acronyms**

GCS	= Glasgow Coma Scale
ISS	= Injury Severity Score
LOS	= length of stay
MODS	= multiple organ dysfunction syndrome
OR	= odds ratio
PRBC	= packed RBC

by our understanding of the high rates of early coagulopathy seen after trauma, present in one-quarter of injured patients after their injury.<sup>8,23,24</sup> Technically, early infusion is feasible, with the availability of immediate release, pre-thawed plasma. Practically, because it is difficult to accurately predict who will need a massive transfusion and, therefore, benefit from aggressive plasma infusion, initiating plasma transfusion immediately in parallel with the 1st unit of blood being infused, irrespective of whether or not a massive transfusion is anticipated, would simplify trauma resuscitation protocols.

However, the impact of plasma administration on injured patients who do not end up requiring a massive transfusion is not known. In fact, plasma in critically ill patients has been associated with increased risk of complications, both infectious and inflammatory.<sup>25-29</sup>

The objective of this study was to determine the outcomes (in-hospital mortality and complications) of plasma administration in trauma patients who required blood but did not undergo a massive transfusion. Our hypothesis was that plasma does not improve survival in this patient cohort and can increase complications.

## METHODS

After IRB approval, a retrospective review of the institutional trauma registry and the Blood Bank Database at the Los Angeles County and University of Southern California Medical Center was performed. All trauma patients admitted to the surgical ICU who received a PRBC transfusion between 2000 and 2005 were identified. Nonmassively transfused patients were defined as those receiving <10 U PRBC during the initial 12 hours after hospital admission. Patients who died within the first 24 hours after hospital admission were excluded from the analysis to minimize the impact of survival bias.<sup>30</sup> Patient variables abstracted included age, gender, injury mechanism, admission vital signs, Glasgow Coma Scale (GCS), Injury Severity Score (ISS), Abbreviated Injury Scale, type and volumes of blood products transfused, ICU length of stay (LOS), hospital LOS, complications (ARDS, multiple organ dysfunction syndrome [MODS], pneumonia, sepsis, line sepsis, bacteremia and fungemia, and acute renal failure), and mortality.

Continuous variables were dichotomized using the following clinically relevant cut points: age (55 years or older versus younger than 55 years), systolic blood pressure at admission (<90 mmHg versus ≥90 mmHg), GCS at admission (≤8 versus >8), ISS (≥25 versus <25), and Abbreviated Injury Scale (≥3 versus <3).

The nonmassively transfused patients were divided into 2 cohorts; patients who received plasma during the first 12 hours after admission and those who received none. These 2 cohorts were compared for differences in demographics, clinical characteristics, and blood transfusion requirements using bivariate analysis. Chi-square or Fisher's exact tests were used to compare proportions and unpaired Student's *t*-test or Mann-Whitney U tests were used to compare means.

Primary outcome measure of this study was in-hospital mortality; the secondary measures were in-hospital complications, ventilation days, ICU LOS, and hospital LOS.

Because the number of confounders was large in comparison with the number of events, patients receiving plasma were matched in a 1:1 ratio to patients who did not receive plasma using propensity scores.<sup>31</sup> Included in the propensity score model were all variables that differed significantly (at the *p* < 0.05 level) between the plasma and no plasma cohorts (injury mechanism, ventilator requirements, systolic blood pressure and GCS on admission, ISS, Abbreviated Injury Scale, total volumes of PRBC, platelets, and cryoprecipitate received at 12 and 24 hours and during the total hospital stay).

Propensity scores (predicted probability of receiving plasma) were calculated for all patients using binary logistic regression. Each patient receiving plasma was matched to a patient who did not receive plasma within a 0.1 caliper of propensity without replacement. The caliper was equal to one-quarter of an SD of the logit of the propensity score (caliper was  $0.38/4 \approx 0.1$ ).<sup>32</sup> Plasma patients for whom no suitable match could be found were excluded from the analysis.

The 2 matched groups were then compared for differences in demographics, clinical characteristics, and blood transfusion requirements. McNemar's chi-square test was used to compare proportions and paired Student's *t*-test was used to compare means.

Outcomes between the 2 matched cohorts were compared using McNemar's chi-square test for proportions and Wilcoxon test for matched sample for means.

Matched patients who received plasma in the first 12 hours were analyzed according to the plasma-to-PRBC ratio received (low [<1:3], medium [≥1:3 and <1:1], and high [≥1:1]). In-hospital survival was compared among these 3 groups. Binary logistic regression was used to adjust

for demographic and clinical differences (ventilation requirements, systolic blood pressure on admission and ISS) among the patients in the groups.

All analysis were performed with SPSS for Windows, version 16.0 (SPSS, Inc).

## RESULTS

During the 6-year study period, 1,993 (69.4%) of the 2,871 trauma patients admitted to the surgical ICU received a PRBC transfusion. Nonmassive transfusion occurred in 1,716 (86.1%) of the transfused patients. After exclusion of 31 (1.8%) early deaths, 1,685 patients were available for analysis. Of those, 516 (30.6%) received plasma during the first 12 hours and 1,169 (69.4%) did not. After propensity score matching, 284 matched pairs were available for analysis (Fig. 1).

The average age of matched patients was  $36.2 \pm 19.4$  years old and 76.8% were male. At admission, 9.6% of the patients were hypotensive (systolic blood pressure  $<90$  mmHg), 37.4% had a GCS  $\leq 8$ , and 46.8% had an ISS  $\geq 25$ . The demographic and clinical characteristics of the study population before and after matching are summarized in Table 1.

Matched patients received a mean of  $2.9 \pm 2.2$  U PRBC in the first 12 hours,  $3.8 \pm 2.7$  U in the first 24 hours, and  $7.7 \pm 6.2$  U during their total hospital stay. The mean number of units of apheresis platelets and cryoprecipitate transfused during their hospital stay was  $0.7 \pm 2.2$  U and  $1.0 \pm 4.0$  U, respectively. Patients who received plasma in

the first 12 hours had a mean of  $3.0 \pm 2.0$  U transfused in the first 12 hours,  $3.7 \pm 2.5$  U in the first 24 hours, and  $6.3 \pm 7.2$  U during their total hospital stay. Patients who did not receive plasma in the first 12 hours had a mean of  $0.6 \pm 1.5$  U plasma transfused in the first 24 hours and  $2.1 \pm 4.8$  U during their total hospital stay (Table 2).

When outcomes were compared between matched patients who received plasma in the first 12 hours and those who did not, there was no difference in ventilation days, ICU LOS, or hospital LOS. Plasma transfusion in those patients who received  $<10$  U PRBC in the first 12 hours also was not associated with improved in-hospital mortality (17.3% plasma versus 14.1% no-plasma;  $p = 0.30$ ). However, those patients who received plasma had a significantly higher rate of overall complications when compared with those who received no plasma (26.8% versus 18.3%; odds ratio [OR] = 1.7; 95% CI, 1.1–2.4;  $p = 0.016$ ). When the volume of plasma transfused was analyzed, there was an increase in complication rates with increasing plasma transfusion in the first 12 hours, with a complication rate of 37.5% for patients receiving in excess of 6 U (Fig. 2). Those patients who received plasma also had a significantly higher incidence of ARDS (9.9% versus 3.5%; OR = 3.0; 95% CI, 1.4–6.2;  $p = 0.004$ ) and a trend toward higher rates of MODS, pneumonia, and sepsis (Table 3). Compared with patients who received no plasma, the risk of ARDS was 4-fold higher for patients receiving 4 to 6 U plasma and 12-fold higher if patients received in  $>6$  U plasma (Fig. 3). The risk of MODS was increased 6-fold if patients received

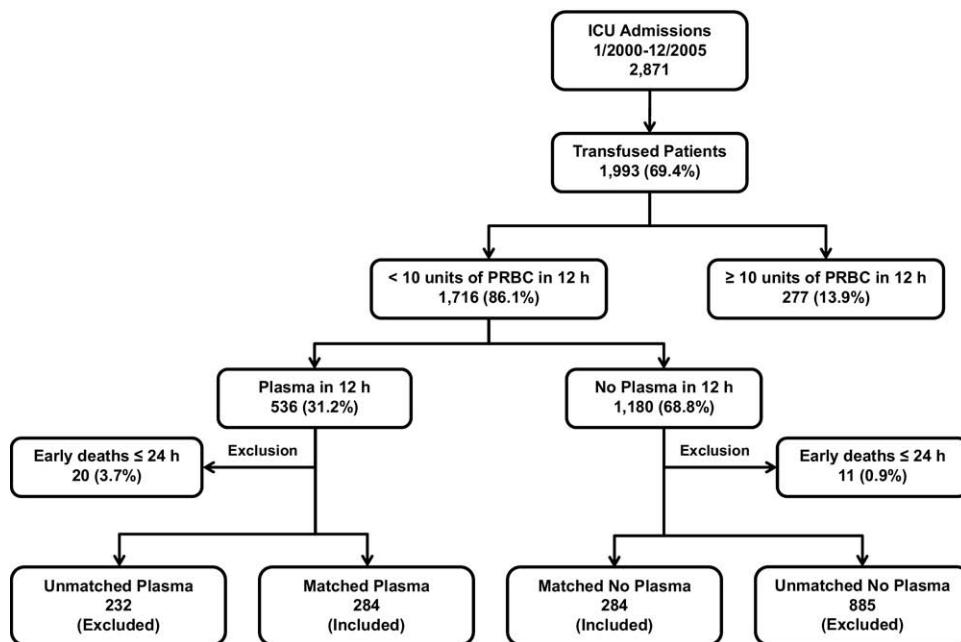


Figure 1. Study outline.

**Table 1.** Demographic and Clinical Data of Patient Groups in Unmatched and Matched Populations

	Unmatched			Matched		
	Plasma in 12 h (n = 516)	No plasma in 12 h (n = 1,169)	p Value	Plasma in 12 h (n = 284)	No plasma in 12 h (n = 284)	p Value
Age (y), mean $\pm$ SD; median (range)	36.5 $\pm$ 19.6; 30 (1–99)	37.9 $\pm$ 19.0; 34 (1–101)	0.18	36.6 $\pm$ 20.7; 30 (1–99)	35.9 $\pm$ 18.1; 31 (1–94)	0.63
Age 55 years or older, %	18.2	18.7	0.84	19.0	17.3	0.59
Male, %	77.9	75.2	0.23	76.8	76.8	>0.99
Blunt, %	56.5	69.6	<0.001	60.1	63.3	0.45
Ventilated, %	91.5	70.8	<0.001	87.7	87.3	>0.99
SBP on admission <90 mmHg, %	14.7	7.5	<0.001	9.3	9.9	0.80
GCS on admission $\leq$ 8, %	36.6	20.5	<0.001	38.5	36.3	0.61
ISS, mean $\pm$ SD; median (range)	25.5 $\pm$ 13.6; 25 (1–75)	19.3 $\pm$ 11.4; 17 (1–75)	<0.001	23.6 $\pm$ 12.8; 22 (1–75)	22.6 $\pm$ 12.1; 22 (1–75)	0.26
ISS $\geq$ 25, %	51.9	30.4	<0.001	47.9	45.8	0.61
Head AIS $\geq$ 3, %	42.6	30.5	<0.001	46.1	41.2	0.27
Chest AIS $\geq$ 3, %	44.8	37.6	0.005	43.7	38.4	0.23
Abdomen AIS $\geq$ 3, %	40.5	25.5	<0.001	33.5	31.0	0.53
Extremity AIS $\geq$ 3, %	27.7	34.0	0.010	25.4	30.3	0.23

Patients were matched for the variables that were significantly different, and for the volume of packed red blood cells, platelets, and cryoprecipitate transfused. For the unmatched cohorts, p values for categorical variables were derived from chi-square and Fisher's exact tests; p values for continuous variables were derived from unpaired Student's *t*-test and Mann-Whitney U tests. For the matched cohorts, the p values for categorical variables were derived from McNemar's chi square test; p values for continuous variables were derived from paired Student's *t*-test.

AIS, Abbreviated Injury Scale; GCS, Glasgow Coma Scale; ISS, Injury Severity Score; SBP, systolic blood pressure.

>6 U plasma (Fig. 4). The risks of pneumonia and sepsis were also increased 4-fold in the patients who received >6 U plasma (Figs. 5 and 6).

When matched patients who received plasma in the first 12 hours were analyzed according to the plasma-to-PRBC ratio received, there was no significant improvement in survival with increasing plasma-to-PRBC ratio: 83.7% for low, 87.8% for medium, and 77.5% for high, adjusted p value for trend = 0.11.

## DISCUSSION

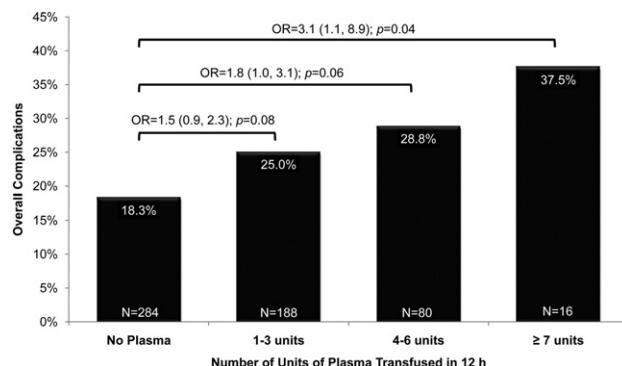
Uncontrolled blood loss is the primary cause of preventable deaths after trauma.<sup>33–35</sup> Although not universally

accepted<sup>30,36,37</sup> and awaiting prospective validation, for patients requiring a massive transfusion, commonly defined as  $\geq$ 10 U PRBC within the first 6 to 24 hours, the majority of data from both military<sup>6–8</sup> and civilian centers,<sup>9–17</sup> including a recently published multicenter study by Holcomb incorporating data from 16 Level I trauma centers,<sup>10</sup> demonstrates improved survival with the aggressive transfusion of plasma in ratios approaching 1:1. The optimal timing, however, for initiation of this aggressive strategy of plasma transfusion is unknown. Published data apply only to patients who end up receiving a massive transfusion, and the role of earlier plasma transfusion in patients who require blood but not in the amounts that would constitute a

**Table 2.** Transfusion Requirements of Patient Groups

	Total (n = 568)	Plasma in 12 h (n = 284)	No plasma in 12 h (n = 284)	p Value
Mean units of PRBC received				
0–12 h	2.9 $\pm$ 2.2; 3 (0–9)	3.0 $\pm$ 2.0; 3 (0–9)	2.8 $\pm$ 2.3; 2 (0–9)	0.41
0–24 h	3.8 $\pm$ 2.7; 4 (0–24)	3.8 $\pm$ 2.2; 4 (0–9)	3.9 $\pm$ 3.1; 4 (0–24)	0.59
Total hospital stay	7.7 $\pm$ 6.2; 6 (1–43)	7.4 $\pm$ 5.9; 6 (1–43)	7.6 $\pm$ 6.6; 6 (1–35)	0.79
Mean units of plasma received				
0–12 h	1.5 $\pm$ 2.1; 1 (0–18)	3.0 $\pm$ 2.0; 2 (0–18)	—	—
0–24 h	2.1 $\pm$ 2.6; 2 (0–18)	3.7 $\pm$ 2.5; 3 (1–18)	0.6 $\pm$ 1.5; 0 (0–8)	<0.001
Total hospital stay	4.2 $\pm$ 6.4; 2 (0–66)	6.3 $\pm$ 7.2; 4 (1–66)	2.1 $\pm$ 4.8; 0 (0–31)	<0.001
Mean units of platelets received	0.7 $\pm$ 2.2; 0 (0–34)	0.7 $\pm$ 1.4; 0 (0–10)	0.7 $\pm$ 2.8; 0 (0–34)	>0.99
Mean units of cryoprecipitate received	1.0 $\pm$ 4.0; 0 (0–33)	1.2 $\pm$ 4.0; 0 (0–22)	0.9 $\pm$ 4.0; 0 (0–33)	0.31

All values are described as mean  $\pm$  SD; median (range). The p values were derived from paired Student's *t*-test. PRBC, packed RBC.



**Figure 2.** Overall complication rates stratified by the number of units of plasma transfused in 12 hours. OR, odds ratio (95% confidence interval); p-values were derived from McNemar's chi-square test.

massive transfusion remains unclear. Because of the survival advantage conferred by aggressive factor replacement in the massively transfused, and the suggestion that the greatest impact can be obtained early on, within the first 6 hours,<sup>10,13</sup> early infusion of plasma, even before the patient declaring themselves as needing a massive transfusion would seem to be a valid treatment option. This study demonstrates that a substantial number of injured patients treated at our facility who did not undergo massive transfusion did, in fact, receive aggressive plasma infusion in ratios that approached 1:1. This has been driven, in part, by the inherent difficulty in predicting who will require a massive transfusion and the perceived importance of not falling behind in factor replacement. Early access to plasma in the resuscitation area and operating room is no longer a limiting factor with the availability of prethawed plasma, which allows for immediate release of liquid plasma on demand.

In theory, early plasma transfusion would seem appropriate for these patients because early coagulopathy after trauma is common. Brohi and Macleod and their colleagues have both independently demonstrated that upwards of one-quarter of patients arrive to the hospital with laboratory evidence of coagulopathy.<sup>23,24</sup> Similar findings have been confirmed by Niles and colleagues in combat casualties.<sup>8</sup>

However, transfusion of plasma is not without consequences.<sup>38-40</sup> There is a fixed cost associated with use of plasma and, perhaps more important clinically, are the associated complications, both infectious and inflammatory. With regard to infectious complications, in a prospective study of a cohort of critically ill trauma patients from the Baltimore Shock Trauma group,<sup>25</sup> after risk adjustment, plasma transfusion was associated with an increase in all infections, with a substantial cumulative increase in this risk for every unit of plasma infused. In a separate prospective analysis,<sup>26</sup> all blood components, specifically including plasma, were found to be associated with an increase in ventilator-associated pneumonia with an adjusted OR of 3.3 (95% CI, 1.2-9.4; p = 0.023). The group at the University of Pennsylvania examined the effects of plasma transfusions in a critically ill surgical ICU population and found that after controlling for other risk factors, there was a significant association between plasma transfusion and infection with an OR of 1.04 (95% CI, 1.01-1.07; p < 0.01) per unit transfused, similar to the magnitude of the effect seen for each unit of PRBC transfused.<sup>27</sup> For inflammatory complications, in a retrospective study of critically ill patients requiring mechanical ventilation for >48 hours, plasma transfusion was associated with development

**Table 3.** Outcomes between Patient Groups

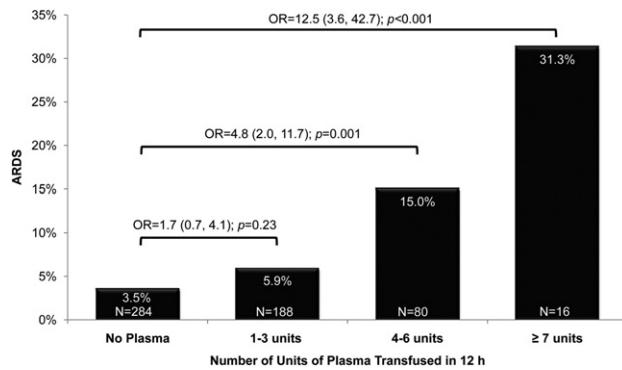
	Total (n = 568)	Plasma in 12 h (n = 284)	No plasma in 12 h (n = 284)	Odds ratio (95% CI)	p Value*
Mortality, %	15.7	17.3	14.1	1.3 (0.8-2.0)	0.30
Overall complication, %	22.5	26.8	18.3	1.7 (1.1-2.4)	0.016
ARDS, %	6.7	9.9	3.5	3.0 (1.4-6.2)	0.004
MODS, %	6.7	8.5	4.9	1.8 (0.9-3.5)	0.13
Pneumonia, %	9.2	11.3	7.0	1.7 (0.9-3.0)	0.11
Sepsis, %	7.4	9.5	5.3	1.9 (1.0-3.6)	0.08
Line sepsis, %	1.8	2.1	1.4	1.5 (0.4-5.4)	0.75
Bacteremia and fungemia, %	3.3	3.5	3.2	1.1 (0.5-2.8)	>0.99
ARF, %	2.3	3.2	1.4	2.3 (0.7-7.5)	0.27
Ventilation, d	6.7 ± 11.2; 3 (0-134) <sup>†</sup>	6.8 ± 10.6; 3 (0-95) <sup>†</sup>	6.7 ± 12.7; 2 (0-134) <sup>†</sup>	0.2 (-2.0 to 1.7) <sup>‡</sup>	0.87
ICU, d	10.6 ± 12.9; 5 (1-118) <sup>†</sup>	10.8 ± 13.3; 6 (1-118) <sup>†</sup>	10.3 ± 12.7; 5 (1-101) <sup>†</sup>	0.5 (-2.7 to 1.7) <sup>‡</sup>	0.20
Hospital, d	19.8 ± 23.2; 15 (1-304) <sup>†</sup>	19.7 ± 23.7; 13 (1-211) <sup>†</sup>	19.9 ± 22.6; 14 (1-304) <sup>†</sup>	-0.2 (-2.6 to 1.6) <sup>‡</sup>	0.99

\*The p values for categorical variables were derived from McNemar's chi-square test, and the continuous variables were derived from Wilcoxon matched pair test.

<sup>†</sup>Mean ± SD; median (range).

<sup>‡</sup>Mean difference (95% CI).

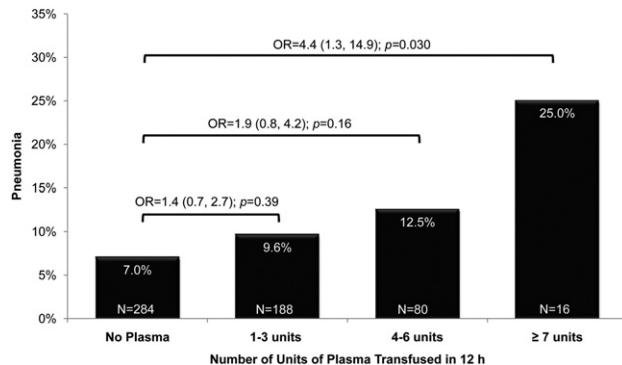
ARF, acute renal failure; MODS, multiple organ dysfunction syndrome.



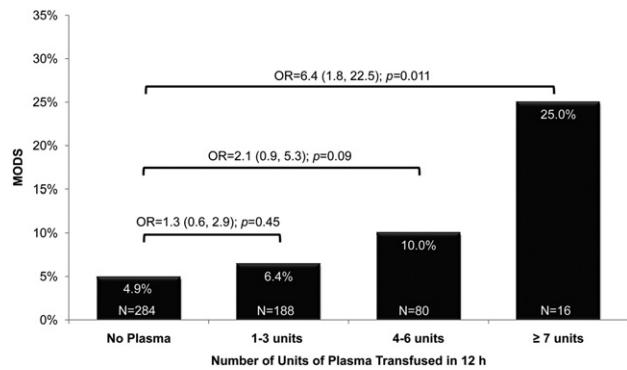
**Figure 3.** ARDS rates stratified by the number of units of plasma transfused in 12 hours. OR, odds ratio (95% confidence interval); p-values were derived from McNemar's chi-square test.

of ARDS.<sup>28</sup> Finally, in a separate study of critically ill non-trauma patients, acute lung injury and ARDS were considerably more likely to develop in patients who received a plasma transfusion.<sup>29</sup>

For patients requiring a massive transfusion, with a focus on mortality as a primary outcomes measure, the description of complications associated with aggressive plasma use has been mixed. In a recent study from the Host Response to Injury Large Scale Collaborative Program database,<sup>11</sup> in patients requiring a massive transfusion, increasing plasma transfusion was associated with improved survival but also increased incidence of ARDS. However, in a separate analysis from Vanderbilt, the institution of a massive transfusion protocol with aggressive plasma use was demonstrated to be associated with a decreased risk of multiorgan failure and infectious complications.<sup>41</sup> The latter study was designed as a longitudinal before-and-after study and the decrease noted might have been due, in part, to the overall decline in the incidence of ARDS.<sup>42,43</sup> For these patients requiring a massive transfusion, however, this potential increase in inflammatory complications is acceptable provided there is an overall survival advantage.



**Figure 5.** Pneumonia rates stratified by the number of units of plasma transfused in 12 hours. OR, odds ratio (95% confidence interval); p-values were derived from McNemar's chi-square test.

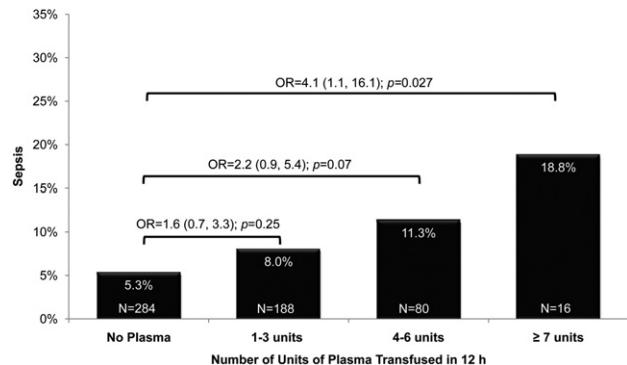


**Figure 4.** Multiple organ dysfunction syndrome rates stratified by the number of units of plasma transfused in 12 hours. OR, odds ratio (95% confidence interval); p-values were derived from McNemar's chi-square test.

Our study was designed to analyze those patients who did not require a massive transfusion. In these patients, there was a substantial increase in complications overall, and ARDS in particular, with no improvement in survival. The incidence of MODS, pneumonia, and sepsis were all increased, with a 6-fold increase for MODS and a 4-fold increase for pneumonia and sepsis in patients who received  $>6$  U plasma. For these patients, the complications associated with plasma transfusion outweighed any potential benefit to survival.

This study was limited by its retrospective design. All complications were captured by a team of experienced nurses in real time, however, the potential for errors in identification and data entry does exist. It is expected that this would have affected both comparison groups equally.

As for the complications themselves, the criteria used to diagnose ARDS were as follows:  $\text{PaO}_2/\text{FiO}_2 \leq 200$ ; chest radiography showing bilateral infiltrates; no evidence of cardiac failure (ie,  $\text{PaOP} \leq 18 \text{ mmHg}$ ) on pulmonary artery catheter or by echocardiography or clinical examination.



**Figure 6.** Sepsis rates stratified by the number of units of plasma transfused in 12 hours. OR, odds ratio (95% confidence interval); p-values were derived from McNemar's chi-square test.

tion. It is known, however, that transfusion-related acute lung injury can have an identical presentation to ARDS. In the present study, we could not establish a definitive temporal relationship between plasma transfusion and development of the complications, which prevented us from making the diagnosis of transfusion-related acute lung injury.

In our previous analysis,<sup>12,44</sup> blood component transfusion data were found to be highly inaccurate in a trauma registry, especially with respect to the volumes infused. Consequently, transfusion data for this study were abstracted exclusively from the Blood Bank, where dispensing and use data are regulated by the US Food and Drug Administration under stringent criteria. US Food and Drug Administration regulations mandate that blood banks maintain records for each unit dispensed and it is hoped that this decreased the errors inherent in this retrospective analysis.

What was not available for analysis was the total crystalloid load received by the patients during their initial resuscitation. As resuscitation strategies using crystalloids can impact neutrophil activation,<sup>45,46</sup> although crystalloid infusion was minimized in both the plasma and nonplasma groups, it is possible that a difference in the volume of crystalloids received by each group might have altered our results.

As consistent base deficit data were not available for analysis, systolic blood pressure was used as a surrogate marker for the shock state in the propensity scoring. This is a measurement that can fluctuate from minute to minute during the initial resuscitation phase and can, therefore, have under- or overestimated the magnitude of shock. Resuscitation is a dynamic process, especially in patients requiring acute blood component replacement. Consequently, clear data on coagulation profiles, their temporal association with transfused products, and recombinant factor 7a use were not available for analysis. Admission international normalized ratio values in particular were missing for approximately 50% of our study population. This is an important limitation that should be considered in any prospective analysis. Regardless of the reason for transfusion, the results remained unchanged, plasma did not improve mortality and increased complications. In addition, pre-existing medications were not available for analysis. Although likely small in number, there might have been patients who were therapeutically anticoagulated on warfarin, for example, that might have benefited from early plasma transfusion.

One of the most important findings of this study is that, in nonmassively transfused patients, plasma does not improve survival, irrespective of the ratio achieved. However,

we performed this analysis not only in the cohort of matched patients, but in the entire cohort of nonmassively transfused patients as well. Results were concordant in both analyses, although the rate of complications was affected by the presence of confounders between the 2 populations that compelled us to match them and control for such differences.

Because of the limited dataset, the exact cutoff at which plasma begins to exert a beneficial effect on survival, outweighing complications, could not be extracted. With the preponderance of retrospective studies available today supporting early plasma transfusion, identifying the number of units of PRBC that should be transfused before plasma is started remains a highly clinically relevant question. It appears that although the bulk of the evidence available today supports the aggressive use of plasma for patients receiving massive transfusions, for patients who received blood but not in massive amounts, plasma does not improve mortality and increases complications. Results of this study support the need for evaluation of the optimal point at which aggressive plasma transfusion should be initiated.

For injured patients requiring a blood transfusion, but <10 U within the first 12 hours, administration of plasma was associated with a substantial increase in overall complications, particularly ARDS, with no differences in in-hospital mortality detected versus control. An increase in MODS, pneumonia, and sepsis was also seen as the amount of plasma these patients received increased. The optimal trigger for initiation of a protocol of aggressive plasma infusion warrants prospective evaluation.

## Author Contributions

Study conception and design: Inaba, Branco, Rhee, Blackbourne, Holcomb, Teixeira, Demetriades

Acquisition of data: Branco, Teixeira

Analysis and interpretation of data: Inaba, Branco, Rhee, Blackbourne, Holcomb, Teixeira, Shulman, Nelson, Demetriades

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